REMARKS

Claims 18-21 and 24-26 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note that the objection to the specification has been withdrawn.

Applicants note that the rejection of claims 18-21 under 35 U.S.C. 112, second paragraph, has been withdrawn.

Applicants note that the cancellation of claims 22 and 23 in the previous response rendered moot the rejection of claims 22 and 23 under 35 U.S.C. 112, second paragraph.

2. Claims 18-21 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to practice the claimed invention. Applicants traverse this rejection.

In the prior Office Action, the Examiner states that "[a]lthough the amended claims may have support for making such invention, the specification does not teach how to use such invention for its disclosed utility." (page 3, lines 7-9). The Examiner further contends that the only disclosed utility is for inducing endothelial remodeling, and maintains the arguments of record regarding the enablement of claims directed to inducing endothelial remodeling.

In accordance with MPEP 2107.01 "to satisfy the requirements of 35 U.S.C. 101, an applicant must claim an invention that is statutory subject matter and must show that the claimed invention is 'useful' for some purpose either explicitly or implicitly." Although Applicants agree that one of the utilities of Applicants' invention is for methods of inducing endothelial remodeling, Applicants strenuously disagree that this is the only utility provided in the application. Exemplary additional utilities that will be discussed in greater detail below include the use of the claimed compositions in screening assays and as an in vitro cell culture system. Furthermore, Applicants point out that utility and enablement must be judged for the **claimed** invention. "The claimed invention is the focus of the assessment of whether an applicant has satisfied the utility requirement. Each claim (i.e., each 'invention'), therefore, must be evaluated on its own merits for compliance with all statutory requirements.....However, regardless of the category of invention that is claimed (e.g., product or process), an applicant need only make one

credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112; additional statements of utility, even if not 'credible,' do not render the claimed invention lacking in utility." (MPEP 2107.02; *Raytheon v. Roper*, 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983)).

In maintaining the rejection based on an alleged lack of enablement, the Examiner appears to disregard the amendments made to the claims in response to the previous Office Action. Given that, as discussed in detail below, the claimed invention has additional utilities that are supported either expressly or inherently by the application, Applicants contend that the enablement of the **claimed invention** must be evaluated. As outlined in detail in MPEP 2107.02, "Office personnel should also be especially careful not to read into a claim unclaimed results, limitations or embodiments of an invention. See *Carl Zeiss Stiftung v. Renishaw PLC*, 945, F.2d 1173, 20 USPQ2d 1094 (Fed. Cir. 1991); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961). Doing so can inappropriately change the relationship of an asserted utility to the claimed invention and raise issues not relevant to examination of that claim."

Applicants agree that one of the utilities of the invention asserted in the application is for inducing endothelial remodeling. However, Applicants disagree with the notion that this is the only utility for the invention that is supported by the application. Applicants direct the Examiner's attention to section II-B of MPEP 2107.02. Although also applied to the situation in which no statement of utility is found within a specification, the guidelines for assessing utility are equally applicable to the present situation in which Applicants contend that the specification supports well-established utilities in addition to the asserted utility of inducing endothelial remodeling.

> "If no statements can be found asserting a specific and substantial utility for the claimed invention in the specification, Office personnel should determine if the claimed invention has a well-established utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. If an invention has a well-established utility, rejections under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph, based on lack of utility should not be imposed." MPEP 2107.02; *In re Folkers*, 344 F.2d 970, 145 USPQ 390 (CCPA 1965)

Additionally, section II-B of MPEP 2107.02 specifies that once Applicants have indicated that the invention has a well-known or implied utility, compliance with 35 U.S.C. 101 and 112 should be evaluated using the same standards as used for evaluating an asserted utility. Guidance from both the MPEP and the courts provides that an "assertion of utility creates a presumption of utility that will be sufficient to satisfy the requirement of 35 U.S.C. 101." (MPEP 2107.02, section III-A; *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (CCPA 1965); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977)).

> "As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope:" (*In re Langer*)

Subsequent cases have echoed the standards set forth in *Langer*, and "direct the Office to presume that a statement of utility made by an applicant is true." (MPEP 2107.02 III-A; *In re Malachowski*, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); *In re Brana*, 5 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995)).

Applicants contend that the claimed invention is not only enabled by the specification, but also that the claimed invention has a number of utilities readily appreciated by one of skill in the art. In addition to the asserted utility of inducing endothelial remodeling, the specification provides extensive inherent support for a variety of well-known utilities for the claimed invention. As outlined in detail above and in MPEP 2107.02 II-B, "[a]n invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible."

Applicants contend that in view of the specification, one of skill in the art would readily appreciate that blood vessels expressing Alk-1 or endoglin have numerous utilities. Exemplary utilities include their use in screening assays to identify agents that affect endothelial cell remodeling, or to provide an in vitro cell culture system of physiologically relevant cells expressing genes important in endothelial development. Such uses are evident to one of skill in the art based on the extensive teachings of the application.

Applicants direct the Examiner to the following portions of the specification which support Applicants' contention that the claimed subject matter has numerous utilities that one of skill in the art would have readily ascertained based on the application: page 3, paragraph 0009; page 5, paragraph 0018-page 7, paragraph 0022; page 12, paragraph 0042; page 13, paragraph 0046. Applicants provide an extensive discussion of the developmental process underlying the formation of endothelial tubes generally, as well as a specific discussion of the involvement of Alk-1 and endoglin in this process. Applicants' discussion of Alk-1 and endoglin is not limited to a mere mention of the possible role of these two proteins in endothelial cells, but also includes extensive guidance as to the relationship between these two important proteins and the TGFβ signaling pathway. Furthermore, Applicants review the state of the art with respect to the phenotype of mice deficient for endoglin or Alk-1 expression.

> "Endoglin is a transforming growth factor-β (TGF-β) binding protein expressed on the surface of endothelial cells. TGF-β signaling is required for vasculogenesis, the first stage of vascular development. During vasculogenesis, the primary capillary network, composed of interconnected and homogeneously sized endothelial tubes, is formed. Indeed, mice lacking endoglin die at an early age due to defective vascular development characterized by poor smooth muscle development and arrested endothelial remodeling. Consequently, endoglin is essential for the second stage of vascular development, angiogenesis, in which the primary endothelial network is remodeled into a mature circulatory system." (page 6, paragraph 0019)

> "The Alk-1 gene encodes a serine/threonine kinase receptor for the TGF-β superfamily of growth factors. The receptor encoded by Alk-1 is highly expressed in the endothelium. Also, loss-of-function mutations of Alk-1 are responsible for a human vascular dysplasia characterized by arteriovenous malformations. Furthermore, anatomical, molecular, and functional distinctions between arteries and veins are lost in mice lacking Alk-1. Lastly, Alk-1 is required for successful embryonic development of distinct arterial and venous vascular beds." (page 6-7, paragraph 0021).

In addition, the specification explicitly teaches a number of methods for expressing a nucleic acid encoding endoglin or Alk-1 in endothelial cells (page 8, paragraph 0031-page 11, paragraph 0040). These methods include, but are not limited to, viral infection and lipid-mediated transfection. Furthermore, the specification teaches endothelial cells and blood vessels

engineered to express exogenously supplied endoglin or Alk-1 (page 12, paragraph 0042; page 13, paragraph 0046).

The specification provides extensive guidance concerning the role of endoglin and Alk-1 in endothelial development, as well as the involvement of endoglin and Alk-1 in TGFβ signaling. Furthermore, the specification provides methods for engineering endothelial cells and blood vessels comprising endothelial cells, and accordingly enables one of skill in the art to practice the claimed invention. Applicants contend that, based upon the present application, one of skill in the art would readily appreciate that the claimed endothelial cells have a number of utilities. Although the induction of endothelial remodeling is one of the utilities discussed in the application, it is in no way the only utility of the claimed invention. Applicants' brief summary of additional utilities for the claimed invention is indicative of the utilities that are readily appreciated by one of skill in the art based on the application as filed. Accordingly reconsideration and withdrawal of this rejection is respectfully requested.

Finally, Applicants wish to point out that the specification explicitly states that the particular embodiments provided in the examples are merely exemplary in nature. "The following description of various preferred embodiments of the invention provides examples of the present invention. The embodiments discussed herein are merely exemplary in nature, and are not intended to limit the scope of the invention in any manner. Rather, the description of these preferred embodiments serves to enable a person of ordinary skill in the relevant art to practice the present invention." (page 4, paragraph 0013). Given the explicit efforts on the part of Applicants to clarify any confusion regarding the limitation of the disclosed subject matter to a single utility, Applicants respectfully submit that it is inappropriate for the Examiner to now erroneously evaluate the claimed invention as if the claimed invention has only a single utility.

Applicants contend that the specification and the state of the art supports Applicants' contention that the claimed invention has multiple utilities, and that the Examiner's evaluation of the enablement of the presently claimed invention should not be limited to an evaluation of whether the claims are enabled for inducing endothelial remodeling. Bearing in mind the ample inherent support for additional utilities for the presently claimed invention, Applicants contend that the **claimed** subject matter, including the amendments expressly added in the previous response, must be analyzed for compliance with the requirements under 35 U.S.C. 112, first paragraph. Since the Office Action indicated that "the amended claims may have support for

making such invention", but that the rejection rested on the Examiner's contention that "the specification does not teach how to use such invention for its disclosed utility", Applicants contend that the above arguments regarding the utility of the presently claimed invention render moot the reasoning underlying the rejection under 35 U.S.C. 112, first paragraph.

In accordance with MPEP 2164.04 and with recent case law, "the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention" (MPEP 2164.04; *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

> "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is some reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (MPEP 2164.04; *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)).

Applicants contend that there is no reasonable basis to question the enablement of the presently claimed subject matter, and the Office Action has provided no reasoning to support a rejection on this ground. As outlined in detail above, the specification provides extensive teachings regarding the making and using of endothelial cells expressing Alk-1 or endoglin. These teachings include the disclosure of multiple methods of expressing exogenous nucleic acids in cells (page 8, paragraph 0031 – page 11, paragraph 0040). In accordance with MPEP 2164.01(b), "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112, first paragraph is satisfied." (MPEP 2164.01(b); *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)). Applicants have amply satisfied this requirement. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: June 30, 2003

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